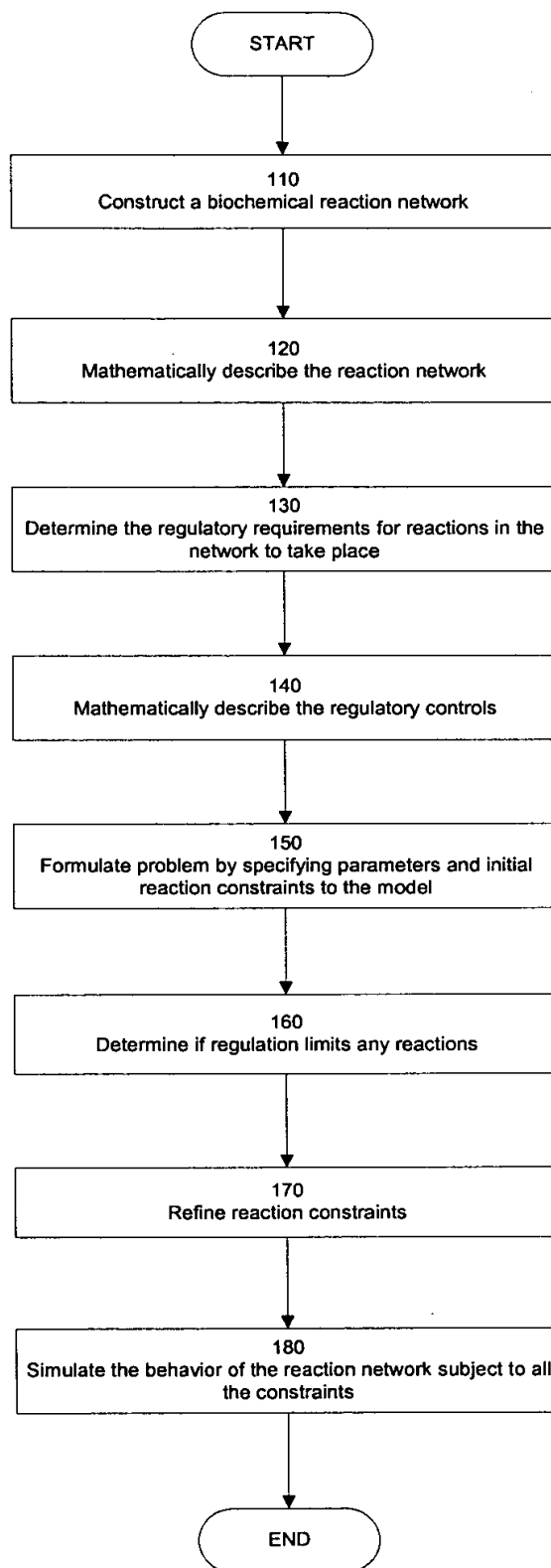


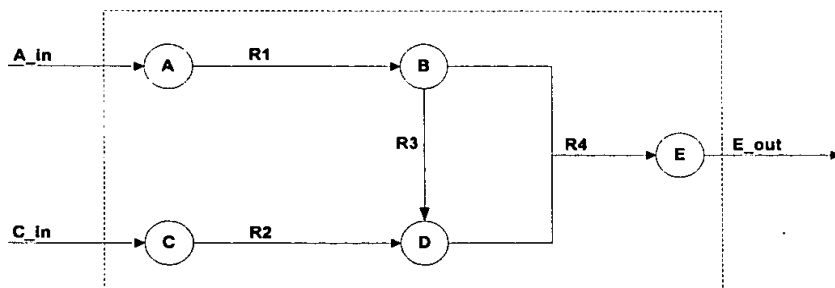
Figure 1

100  
General Process for Developing and Implementing  
a Regulated Biochemical Reaction Network Model

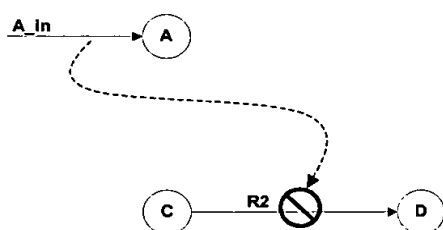


# Figure 2

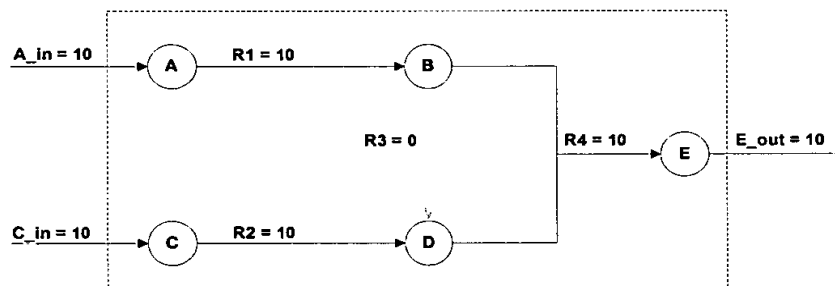
## A) Example Biochemical Reaction Network



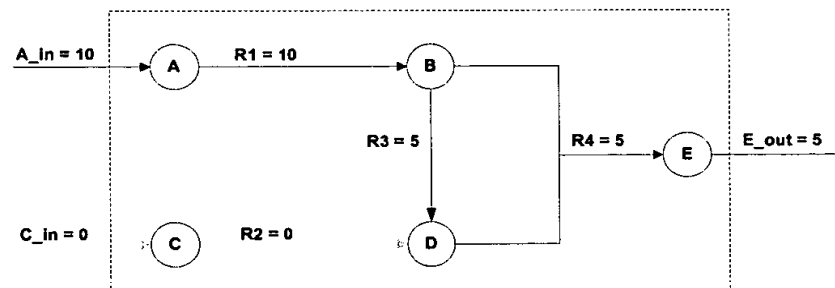
## B) Example Regulatory Structure and Requirements



## C) Simulated Reaction Network (without regulation)

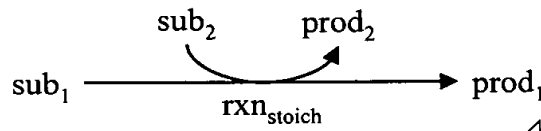


## D) Simulated Reaction Network (with regulation)

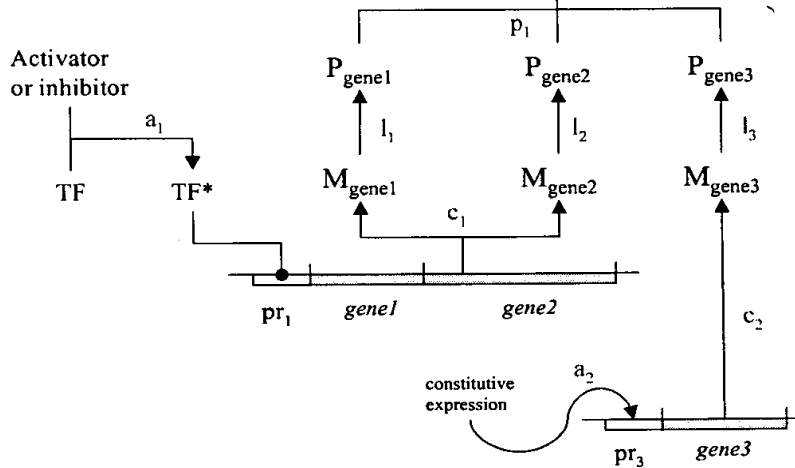
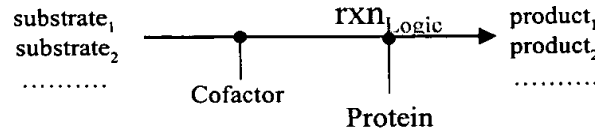


# Figure 3

## Metabolic Model



## Regulatory Model



- Activity constraints set for  $rxn_{stoich}$   
(lower bound = 0, upper bound = INF or #)
- Inactivity constraints for  $rxn_{stoich}$   
(lower bound = 0, upper bound = 0)

**Integration of Stoichiometric model and Logical model** achieved through regulatory restraints (logic values of reaction processes) which are used to refine appropriate reaction constraints in the model:

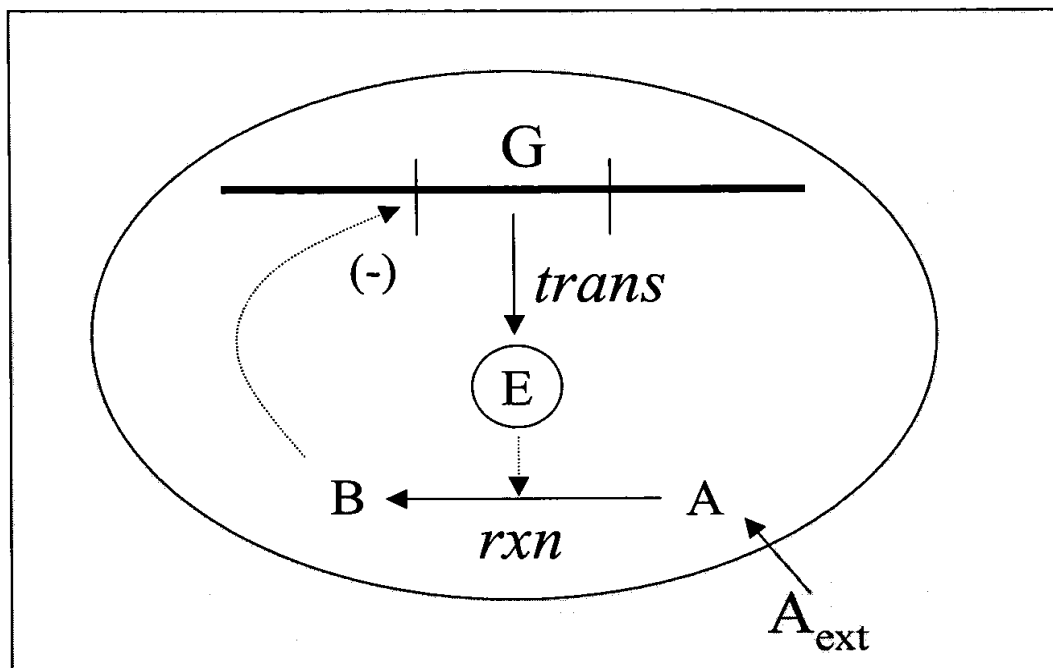
If  $rxn_{Logic} = 1$  then use Activity constraints  
If  $rxn_{Logic} = 0$  then use Inactivity constraints

### Logic functions

$a_1 = (\text{activator/inhibitor}) \cdot TF$   
 $a_2 = 1$   
 $c_1 = TF^* \cdot pr_1 \cdot gene1 \cdot gene2$   
 $c_2 = pr_3 \cdot gene3$   
 $l_1 = M_{gene1}$   
 $l_2 = M_{gene2}$   
 $l_3 = M_{gene3}$   
 $p1 = P_{gene1} \cdot P_{gene2} \cdot P_{gene3}$   
 $rxn_{Logic} = \text{Protein} \cdot \text{Cofactor} \cdot \text{Substrate}_1 \cdot \text{Substrate}_2$

Time delays can be specified for the switching of each memorization variable after a triggering change in the associated function

Figure 4



bioRxiv preprint doi: <https://doi.org/10.1101/000000>; this version posted January 1, 2014. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY-NC-ND 4.0 International license.

Figure 5

200

A Time-Dependent Implementation of a Regulated  
Biochemical Reaction Network Model

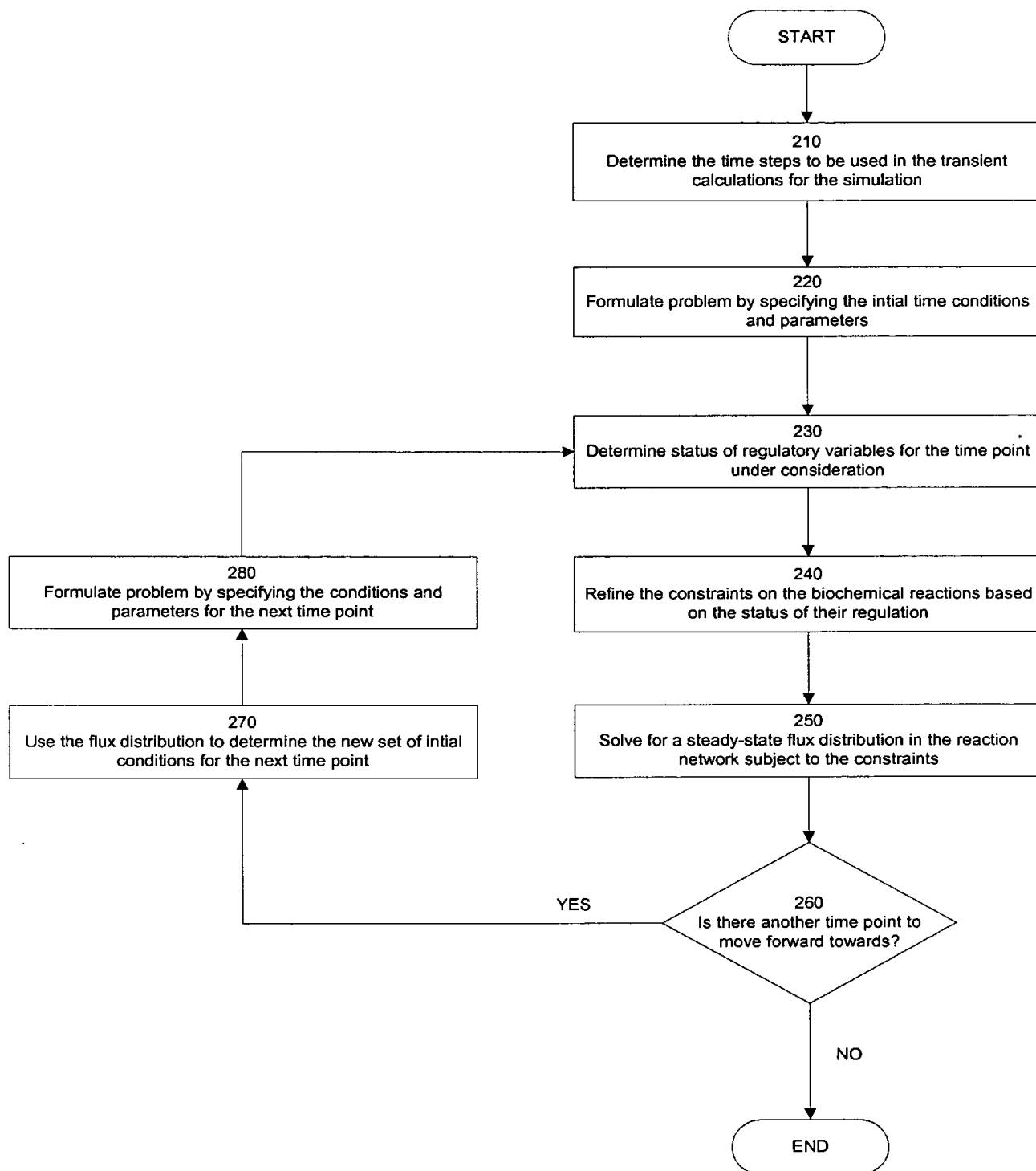
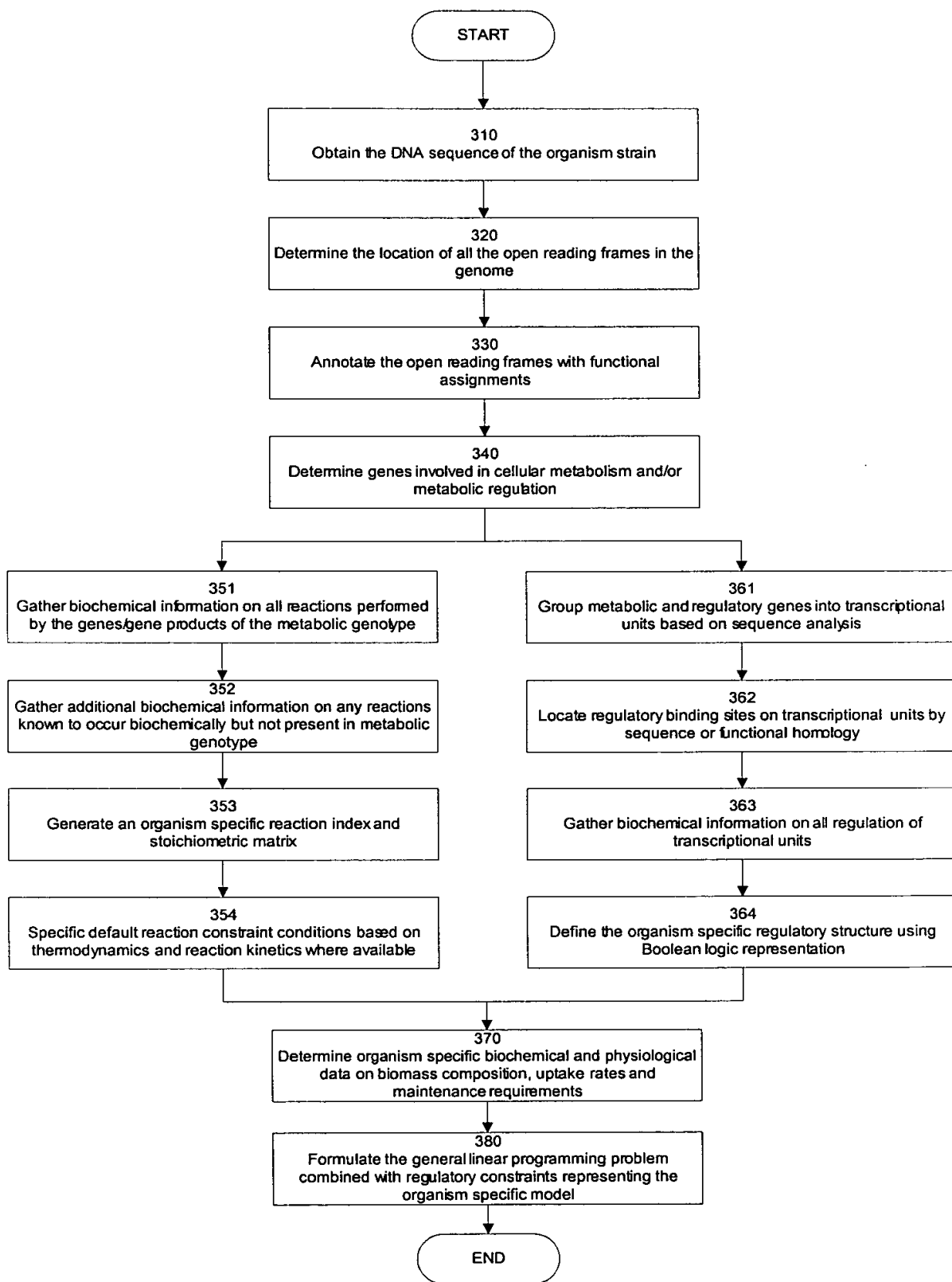
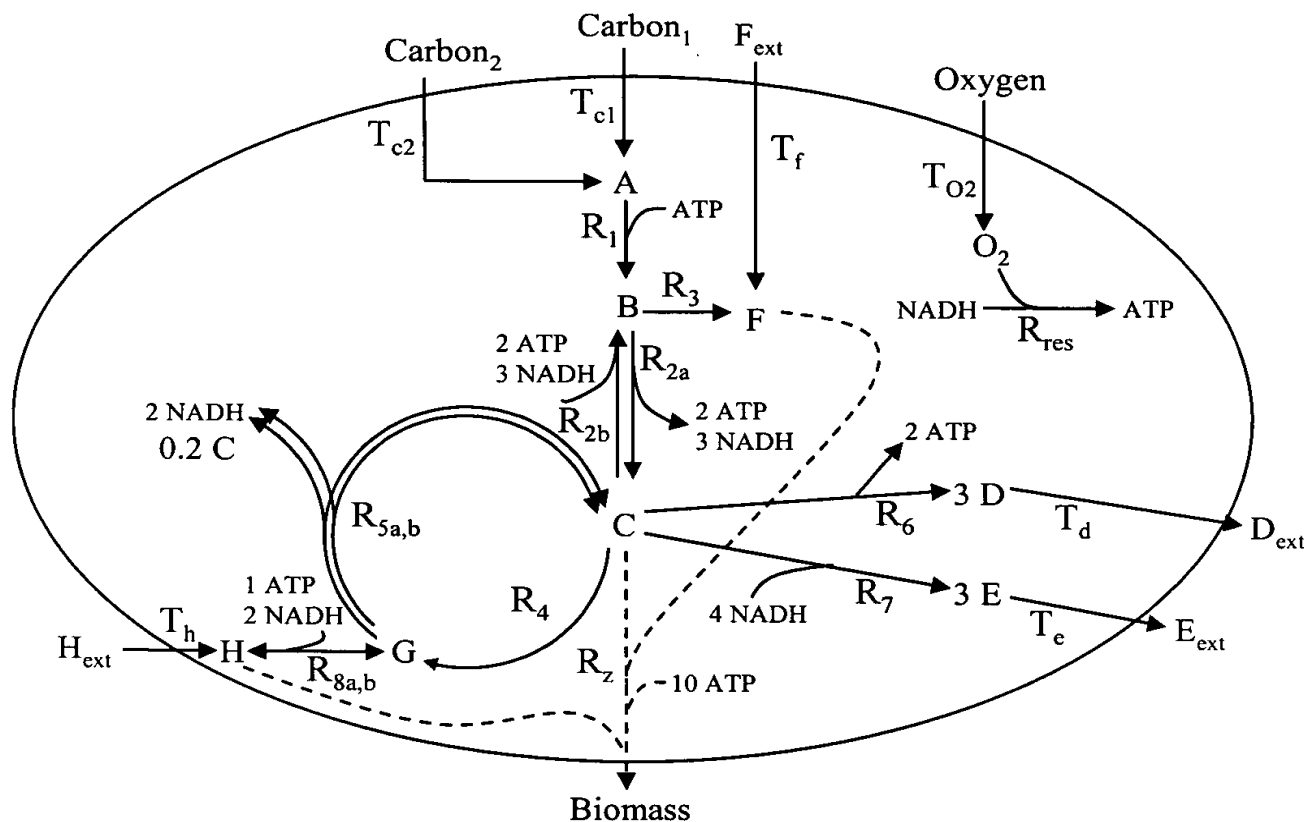


Figure 6

# 300 Process for Developing Genome Scale Regulated Models of Metabolism



# Figure 7



REACTION	NAME	REGULATION
<i>Metabolic Reactions</i>		
-1 A -1 ATP +1 B	R1	
-1 B +2 ATP +2 NADH +1 C	R2a	IF NOT(RPb)
-1 C -2 ATP -2 NADH +1 B	R2b	
-1 B +1 F	R3	
-1 C +1 G	R4	
-1 G + 0.8 C +2 NADH	R5a	IF NOT (RPo2)
-1 G + 0.8 C +2 NADH	R5b	IF RPo2
-1 C +2 ATP +3 D	R6	
-1 C -4 NADH +3 E	R7	IF NOT (RPb)
-1 G -1 ATP -2 NADH +1 H	R8a	IF NOT (RPh)
+1 G +1 ATP +2 NADH -1 H	R8b	
-1 NADH -1 O <sub>2</sub> +1 ATP	Rres	IF NOT (RPo2)
<i>Transport Processes</i>		
-1 Carbon <sub>1</sub> +1 A	Tc1	
-1 Carbon <sub>2</sub> +1 A	Tc2	IF NOT(RPc1)
-1 Fext +1 F	Tf	
-1 D +1 Dext	Td	
-1 E +1 Eext	Te	
-1 Hext +1 H	Th	
-1 Oxygen +1 O <sub>2</sub>	To2	
<i>Maintenance/Growth Processes</i>		
-1 C -1 F -1 H -10 ATP +1 Biomass	Growth	
<i>Regulatory Proteins</i>		
	RPo2	IF NOT(Oxygen)
	RPc1	IF Carbon <sub>1</sub>
	RPh	IF Th
	RPb	IF R2b

Figure 8

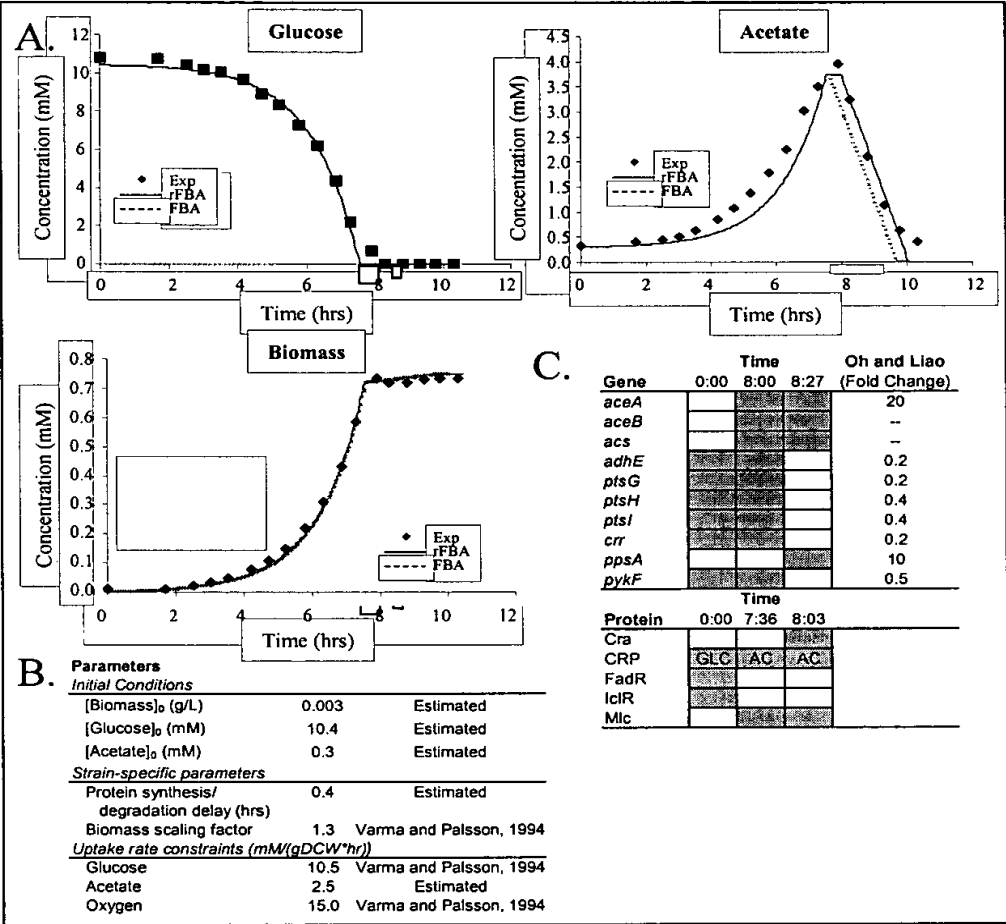


Figure 9

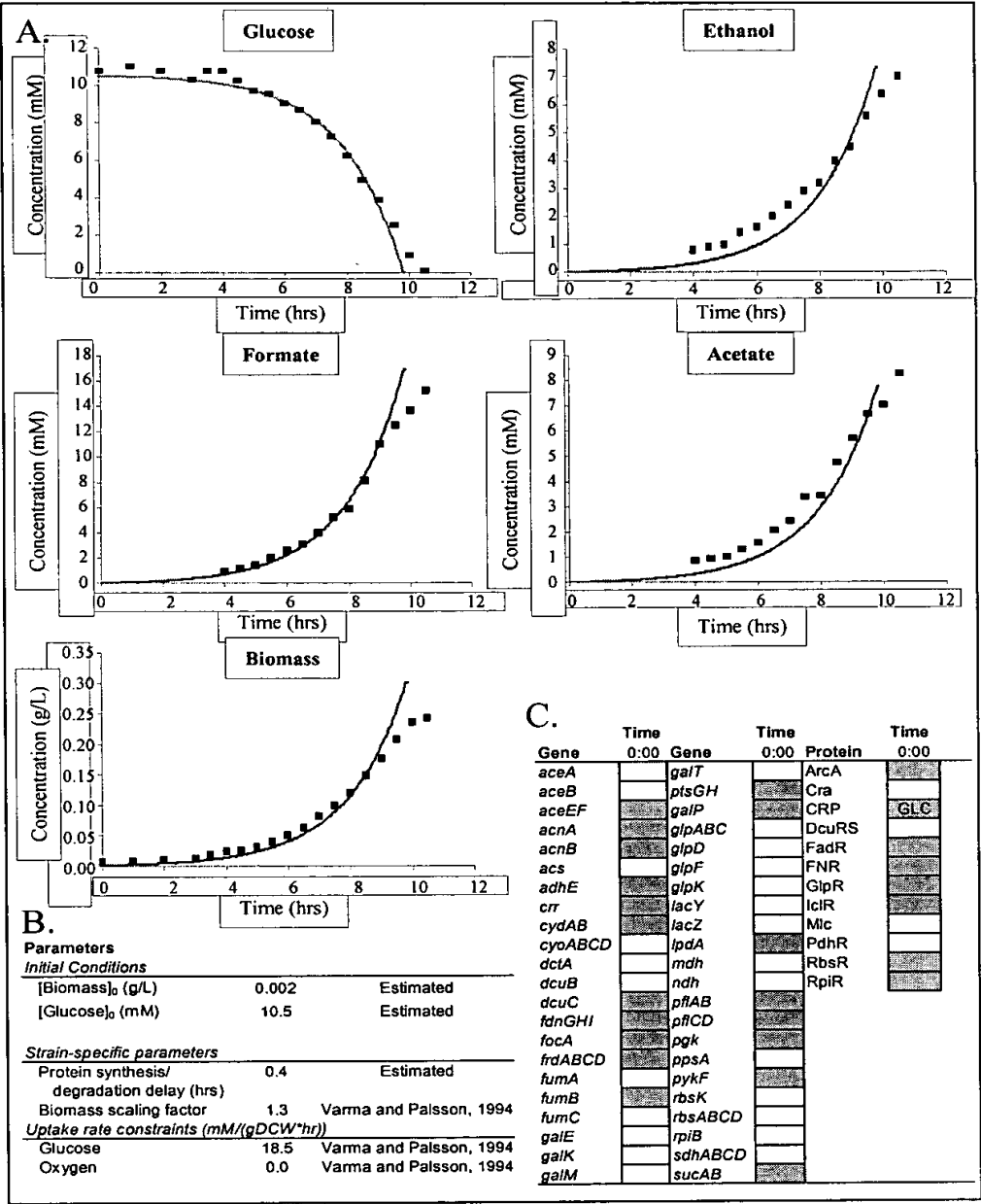


Figure 10

